US Patent Application No. 10/506805
Filed 19 January 2005
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Attorney Docket: Q83534
Examiner: Purdy, Kyle A.

35 U.S.C. 1.132 DECLARATION

I, Andrew Lennard Lewis, a UK citizen of Biocompatibles UK Limited, Chapman House, Farnham Business Park, Weydon Lane, Farnham, Surrey GU9 8QL, UK, declare as follows:

1. I am one of the inventors of this Application. I am currently the Research and Technology Director of Biocompatibles UK Limited ("Biocompatibles"), the assignee of the present Application. I have been at Biocompatibles since 1996, in various roles as Project Manager and Head of Chemistry of the Biomaterials Development Group. I have read the Official Action dated 11 October 2007, and the documents mentioned in that letter.

2. The Examiner has relied on an article by Konno *et al.* published in Biomaterials, 2001, 22, 1883-1889. The Examiner asserts that Konno *et al.* specifically teaches "a nanoparticle comprising a hydrophobic and a hydrophilic block (copolymer)". This is not correct. Konno describes copolymers, formed of a zwitterionic monomer and a hydrophobic monomer. However these monomers are not polymerised so as to form a block copolymer. Instead they are polymerised together to form a random copolymer. Konno *et al.*, in the Materials section, 2.1, describe the copolymerisation as "a conventional radical polymerisation technique using t-butylperoxy neodecanoate as the initiator". Konno *et al.* does not give further details of the polymerisation. However there is a cross reference to an earlier publication by the same group, document 12 in Konno *et al.*, where the same polymers had been previously described. I have reviewed that document, but in fact it gives no further details on the polymerisation, but again describes the polymerisation as being "conventional radical polymerisation in ethanol using AIBN 2,2'-azobisisobutyronitile as an initiator". AIBN is an alternative radical initiator to t-butylperoxy neodecanoate used in Konno *et al.* That, Ishihara 1999 article, itself refers to a yet earlier disclosure by the same group, cross referenced document 10, by Ueda *et al.*, in Polymer Journal, 24(11), 1259-1269 (1992). This reference does indeed give further details of the copolymerisation of MPC with alkyl methacrylates, specifically butylmethacrylate. A copy of Ueda *et al.* is attached as Exhibit ALL1.

3. In the section headed Experimental, on page 1260, under the subtitle "Synthesis in Characterisation of Poly(MPC-co-alkylmethacrylate), the polymerisation is described. The zwitterionic monomer MPC, alklymethacrylate and initiator, AIBN, were co-dissolved in a solvent and pored into a reaction vessel, in this case a "polymerisation tube". The initiator is activated by heating to 60EC. The polymer is recovered by precipitation into a non solvent for the polymer. Since the monomers are all present throughout the polymerisation, they will copolymerise randomly i.e. the polymer will have a random arrangement of units derived from the two comonomers. This is the conventional technique of copolymerisation used by Konno *et al.*

4. In Figure 1 of Konno, the authors illustrate the structure of the copolymer. They draw the unit derived from MPC monomer, and the unit derived from butylmethacrylate. These are surrounded by boxes. Also the carbon atoms which become part of the polymer backbone have parenthesis around them, showing the mole proportion of units in the polymer derived from the respective monomer. Figure 1 does not illustrate a block copolymer. In a block copolymer each "block" comprises multiple units derived from the respective monomer molecules.

5. In Figure 2 of Konno, a schematic representation of a nanoparticle formed from the random copolymer of MPC and butylmethacrylate and polylactic acid. The diagram is intended to show the interaction between monomer units derived from the relatively hydrophobic butylmethacrylate monomer and polylactic acid, while the zwitterionic (PC) group derived from MPC monomer finds itself at the surface of the nanoparticles. Again this Figure does not illustrate a block copolymer of butylmethacrylate and MPC.

6. I am aware that the Ishihara group, from which the Konno *et al.* and Ueda *et al.* papers are derived, has continued to carry out work in various copolymers of MPC, and has investigated the utility of such copolymers to act as drug carriers, in particular for hydrophobic drugs. An article by this group, Yusa, S. *et al.*, Biomacromolecules 2005, 6, 663-670 is attached as Exhibit ALL2. In this publication, random copolymers of MPC and butylmethacrylate are compared side-by-side with block copolymers having MPC blocks and butylmethacrylate blocks, having regard to the polymers ability to take up hydrophobic therapeutic compounds such as paclitaxel. In Yusa *et al.*, the random copolymers are said to be "synthesised by a conventional radical polymerisation and purified by the method reported previously". In the document to which reference is made, the 1999 publication by Ishihara *et al.*, there are in fact no details of the polymerisation, but again merely a cross-reference back to the Ueda *et al.* 1992 reference, ALL1. Thus these seem to be the same random copolymers as are described by Konno *et al.* Polymerisation to form block copolymers requires a more complicated non-conventional technique. In this case the technique of "reversible addition fragmentation chain transfer" (RAFT) was used by Yusa *et al.* Our preferred polymerisation method for forming block copolymers is atom transfer radical polymerisation (ATRP), which is also mentioned by Yusa *et al.* at page 664, left hand column, around half way down the column. The block copolymers have one block formed of units derived only from MPC monomer and another block formed of units derived only from butylmethacrylate. These block copolymers are encompassed within the scope of the claims of the present Application.

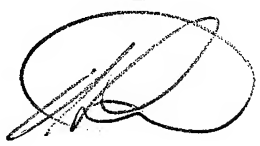
7. Yusa *et al.* compare the properties of the random and block copolymers for solubilisation of paclitaxel. The technique for determining the solubility is described at page 665, right hand column, under the hearing "Determination of PTX Solubility .....". The results are described in Table 2, and on page 669, left hand column, under "Solubilisation of PTX by $pMPC_m$-BMA_n in Aqueous Media". The authors conclude that a much lower concentration of the block copolymer can dissolve the same amount of paclitaxel as the random copolymer, with the same or substantially the same mole fraction of monomers. The authors explain the different properties as being related to the formation of stable domains in this aqueous composition, with hydrophobic domains which solubilise PTX. They also theorise that the micelles may have MPC blocks at the shell, which may interact with biological systems in a favourable manner.

8. The Yusa publication was published in 2005, well after the date on which our first European Application, from which the present Application claims priority, was filed. In an earlier publication, by lead author Konno, in J. Biomed. Mater. Res. 65A:209-214, 2003, some additional details are given of the paclitaxel solubilisation investigations. In this publication, attached as Exhibit ALL3, the random block copolymer of MPC and butylmethacrylate is tested, alongside random copolymers of MPC with other monomer units. This publication also was made available to the public after our first European filing. It has no mention of any MPC block copolymers.

9. Ishihara's group is a respected academic group which has been working on MPC polymers for well over a decade. I believe the results reported in the papers exhibited to this declaration to be true. The results are consistent with our own work at Biocompatibles and the work done by the groups at University of Sheffield headed by my co-inventor Professor S. Armes and Brighton University headed by my co-inventor Professor A. Lloyd on MPC:alkly methacrylate block copolymers and the ability of such copolymers to interact with hydrophobic actives in a beneficial manner.

10. I acknowledge that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. 1001) and may jeopardise the validity of the Application or any Patent issuing thereon. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true.

Dated this 7th day of January 2008



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